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Total Number of Pages in This Submission: 55

Application Number	09/125,841
Filing Date	January 19, 1999
First Named Inventor	Richard G. Olsen
Art Unit	1644
Examiner Name	Ronald B. Schwadron, Ph.D.
Attorney Docket Number	CIR 2-001-3

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
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- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
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- ☑ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) (please Identify below):

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Mueller and Smith, LPA		
Signature			
Printed name	Jerry K. Mueller, Jr.		
Date	March 29, 2005	Reg. No.	27,576

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Signature	Jane Keeney		
Typed or printed name	Jane Keeney	Date	March 29, 2005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Richard G. Olsen, *et al.*
Serial No.	:	09/125,841
Filed:	:	January 19, 1999
For:	:	CELLULAR IMMUNOTHERAPY
TC/AU	:	1644
Examiner	:	Ronald B. Schwadron, Ph.D.
Attorney Docket No.	:	CIR 2-001-3

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APPELLANTS' AMENDED BRIEF ON APPEAL

Sir:

Responsive to a Communication mailed February 27, 2004, and responsive to the Examiner's Notification of Non-compliance mailed March 23, 2005, submitted herewith in triplicate is Appellant's Brief on Appeal as prescribed in 37 C.F.R. § 1.192. Reversal of the primary examiner's rejection of the appealed claims and their allowance is respectfully requested.

The attached brief has been updated to reflect the current Real Party in Interest, as the application was assigned and licensed subsequent to the filing of the original Appeal Brief.

The requisite fee of $165.00 as required in 37 C.F.R. § 1.17(c) was previously submitted. Any additional payments that may be required should be charged to Deposit Account No. 13-4830.

Respectfully submitted,

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Alexandria, VA 22313-1450

Jane Keeney
Jane Keeney

Real Party in Interest

The appealed application was assigned by the Appellant, to Cira Technologies, Inc. Cira Technologies, Inc subsequent to the filing of the Appellant's Brief assigned the application to the current real party in interest Cira, Ltd., an Ohio limited liability company, who has exclusively licensed the application to Cira BioSciences, Inc., a Delaware Corporation owned by Cira, Ltd., and Neoprobe Corporation, a Delaware Corporation.

Related Appeals and Interferences

There are no related appeals or interferences known to applicant, their legal representatives, or assignee that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

Status of Claims

Forty one (41) claims were submitted with the application as originally filed.

An Office Action was mailed on March 28, 2001 imposing a restriction requirement. Appellants elected claims 29-35 in a response mailed May 4, 2001. Claims 1-28 and 36-41 have subsequently been cancelled.

An Office Action was mailed on December 10, 2001 rejecting claims 29-35 under 35 U.S.C. § 112 as being indefinite, and under 35 U.S.C. §103(a) as being obvious. In particular, Babbitt *et al.* (U.S. Patent No. 5,766,920) and separately Ochoa et al., (U.S. Patent No. 5,443,983) were cited as the basis for the §103(a) rejections. responded with amendments to claims 29-35 in a response mailed June 4, 2002. also drew the Examiner's attention to an affidavit by Dr. Pierre Triozzi filed in a related Application No. 08/943,993, to which priority is claimed.

During prosecution there were several problems with the computer readable form of the sequence listing, including software errors, formatting errors, and damage to the submission in transit, despite ' extraordinary attempts to comply with the Sequence Rules. The Examiner issued a notice of abandonment for failure to comply with the Sequence Rules in a paper mailed June 24, 2003. complied with the Sequence rules and petitioned to withdraw the holding of abandonment in a response mailed August 25, 2003. ' Petition was granted and the holding of abandonment was withdrawn by a Notice mailed November 20, 2003.

An Office Action was mailed on February 27, 2004, rejecting all claims, and making the action final. The Examiner again rejected claims 29-35 under 35 U.S.C. § 112 as being indefinite, and under 35 U.S.C. §103(a) as being obvious. Babbitt *et al.* (U.S. Patent No. 5,766,920) and separately Ochoa et al., (U.S. Patent No. 5,443,983) were cited as the basis for the §103(a) rejections. Because the Dr. Triozzi's affidavit that was part of the parent application's file history and with which the Examiner was familiar was not enclosed, neither the affidavit nor the arguments based on the affidavit were considered.

Appellants filed an Amendment and Response After Final by a facsimile on June 28, 2004, amending claims 29-35 in accordance with the Examiner's typographical suggestions. Appellants also submitted a copy of the affidavit of Dr. Triozzi, and requested reconsideration by the Examiner, or in the alternative, entry of the amendments and affidavit for purposes of appeal. Said submissions comply with 37 CFR 1.116, adopt the Examiner's suggestions and or require only a cursory review.

Appellants filed a notice of appeal by mail on June 28, 2004.

In an advisory action mailed November 17, 2004, the proposed amendments were entered and rejected. The previously pending rejection of the claims under 35 USC §112

was withdrawn in view of the amended claims. Even though the affidavit of Dr. Triozzi was already part of the complete file history, and was previously considered by the same Examiner in conjunction with an application to which the instant application claims priority, the Examiner declined to consider the affidavit because it is not directed solely to issues which were newly raised by the Examiner in the final rejection.

Thus, this appeal involves claims 29-35, directed to enriched T helper cell populations derived from patients infected with HIV.

Status of Amendments

Appellants requested entry of amendments to the claims submitted June 28, 2004. The Examiner entered the proposed amendments for purposes of appeal in an advisory action mailed November 17, 2004.

Summary of Invention

The invention is a novel approach to the adoptive cellular therapy of HIV infection that exploits the potentially effective cellular immune response that is initially generated in HIV-infected individuals. Application, p. 7, l. 30-p. 8, l.12. Cytokine-producing cells derived from lymph nodes excised from patients infected with HIV are subjected to mitogenic stimulation for their expansion. One aspect of the invention is a therapeutic agent for treating patients afflicted with HIV. Application p. 11, l.33-p. 12, l.24. The invention also is capable of inhibiting replication of HIV as measured by the viral load reductions exhibited by patients that receive the inventive therapeutic and capable of inducing an immunorestorative effect in HIV patients. Application, p. 12, l. 26-l. 34. Other aspects of the invention are described in the specification , including in the Examples.

Issues

1. Is the invention a nonobvious enriched T helper cell population expanded by subjecting cells derived from lymph nodes excised from patients infected with HIV in light of Babbitt *et al.* (U.S. Patent No. 5,766,920) and Ochoa *et al.*, (U.S. Patent No. 5,443,983)?

2. Is the application in condition for allowance since the oath and declaration are in order and because the Application properly claims of priority?

Grouping of Claims

Claims 29-35 subject to the instant appeal are being treated as a single grouping.

Argument

Summary of the Rejection

Claims 29-35 stand rejected under 35 U.S.C. §103(a) as being obvious in light of Babbitt *et al.* (U.S. Patent No. 5,766,920) and separately Ochoa *et al.*, (U.S. Patent No. 5,443,983).

The oath and declaration was defective because it was not signed by inventor Olsen. The Examiner objected to the Appellants' claim of priority requesting removal of the phrase "based on" and requesting substitution of the phrase "is a 371 of."

1. The invention is a nonobvious enriched T helper cell population expanded by subjecting cells derived from lymph nodes excised from patients infected with HIV .

Claims 29-35 stand rejected under 35 U.S.C. § 103(a) as being obvious over Babbitt *et al.* (U.S. Patent No. 5,766,920). Claims 29-35 also stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Ochoa, *et al.* (U.S. Patent No. 5,443,983). Appellants respectfully traverse the rejections of the claims and grounds therefor.

Appellants teach use of excised lymph node tissue as a source of T helper cells because lymph nodes offer numerous advantages over other tissues as a cell source. Babbitt *et al.* teach use of peripheral blood as a preferred source of T-helper cells, and uses repetitive rounds of a multi-step procedure to co-stimulate the low numbers of T-helper cells present in peripheral blood. Lymph nodes on the other hand, are a complex tissue, enriched in antigen presenting cells, and particularly dendritic cells, both of which are at low concentrations in peripheral blood. Thus, Appellants submit that the invention taught by Babbitt *et al.* does not render obvious the expansion of activated T-helper cells derived from lymph nodes, because the two "tissues," though they share certain cell types, differ in their responses to cytokines and other stimuli. Appellants note that the amended claims do not claim use of peripheral blood lymphocytes as a source of mononuclear cells for the *in vitro* cell manipulation of the invention. Appellants actually teach away from using peripheral blood lymphocytes as a source of T-helper cells, because peripheral blood is ineffective to serve as a source of T-helper cells when used in the method taught in by the Appellants' invention.

The procedure disclosed by Appellants, contrary to that of Babbitt maintains the viability of antigen presenting cells present in lymph nodes. The present invention differs so substantially from that disclosed by Babbitt and offers such substantial improvements in ease of application and reliability that the ' invention is not obvious in light of Babbitt.

The novelty and nonobviousness of the Appellants' invention is emphasized by the affidavit of Dr. Pierre L. Triozzi. Dr. Triozzi, supervising a pilot study implementing an embodiment of the instant invention, reports the results of experiments comparing the cell expansion of $CD4^+$ and $CD8^+$ cells derived from peripheral blood and from excised lymph nodes. These results clearly show that $CD4^+$ and $CD8^+$ cells were expanded to a far lesser degree when the lymphocyte progenitors were derived from peripheral blood lymphocytes than when derived from lymph nodes. ¶ 7, 8 of Dr. Triozzi's December 18, 1997 affidavit. Next, Dr. Triozzi reports the results of cytokine production assays (MIP-1a and RANTES) from cells expanded from lymph node lymphocytes and from peripheral blood lymphocytes. Again, the amount of cytokine produced from the cells expanded from lymph node lymphocytes was significantly greater than from cells expanded from peripheral blood. ¶ 9-11 of Dr. Triozzi's December 18, 1997 affidavit. Thus peripheral blood, as practiced by Babbitt is an inferior source for expansion of $CD4^+$ and $CD8^+$ cells, and for the production of cytokines by these cells.

The use of lymph node lymphocytes results in a much more effective treatment of HIV patients for <u>both</u> reduction of viral load and for restoration of immune function compared to peripheral blood lymphocytes. ¶ 12 of Dr. Triozzi's December 18, 1997 affidavit. These tests demonstrate that lymphocytes derived from such different sources as lymph nodes or peripheral blood do not possess equivalent generative potential. The source of lymphocytes surely impacts their use in adoptive cellular therapy. It is not surprising that prior workers in this field using peripheral blood lymphocytes for adoptive cellular therapy could not effectively treat HIV infection, whereas appellants show a therapeutic benefit.

It is without question that Dr. Triozzi is eminently qualified as an expert in this field. Dr. Triozzi supervised a pilot study, implementing an embodiment of the present invention disclosed and claimed in the application. The affidavit of Dr. Pierre L. Triozzi, was originally submitted in prosecution of the application Ser. No. 08/943,993, which is a continuation of Ser. No. 08/604,728, to which priority of the present application has been claimed. The Examiner, though he was aware of and had access to this affidavit, and though its contents were brought to his attention, declined to consider it during prosecution of the application. Appellants have already submitted a copy of Dr. Triozzi's affidavit, and again request its entry and consideration.

The Appellants' invention is nonobvious in light of Ochoa et al. because Ochoa similarly fails to recognize the advantage of using lymph nodes removed from a patient with HIV as a preferred tissue source. Appellants' invention teaches that excised lymph

nodes from HIV infected patients are a preferred source for the expansion of T-helper cells of the invention. Ochoa is even less relevant that Babbitt, because Ochoa shows no preference for tissue source, so long as lymphocytes can be obtained. Ochoa does not even refer to lymph nodes. Therefore, the advantages of preferring lymph nodes as a tissue source under the Appellants' invention could not have been obvious to Ochoa.

Rather than generating a population of specific T helper cells, what Ochoa is attempting to accomplish is to simply generate "a large number of activated cells" while minimizing toxicity to the patient and avoiding repeated venipunctures. Ochoa, Col. 2, ll. 42-67. It is abundantly clear that Ochoa is not aware of the Appellant's invention, by considering Example 4 of the Ochoa patent. Ochoa collected peripheral blood lymphocytes from the patient's twin brother in attempting to treat HIV. Ochoa, Col. 11, ll. 51-56. The appellants' invention is to use the lymph nodes of the infected patient as a source of cells for culture, rather than the peripheral blood of the uninfected brother. Clearly the advantages of the Appellants' invention are not obvious to Ochoa, because Ochoa's practice is contrary to the Appellants' invention.

Though the disclosures in Babbitt and Ochoa suggest in passing that lymph nodes could be used as a source of lymphocytes, lymph nodes are not a preferred source in the prior art. Indeed, there is no way to predict from the experimental results reported by Babbitt and Ochoa that lymph node lymphocytes would be a preferred, or even an enabling, source for basing an adoptive cellular therapeutic in the treatment of HIV patients. This is especially telling in view of the excellent data, including patient data, presented in the application. As Dr. Triozzi states, "If anything, it may be considered counter-intuitive to use a major reservoir of HIV, *i.e.*, lymph nodes, and the central target of HIV infection, *i.e.*, activated $CD4^+$ cells, in the adoptive cellular therapy of HIV infection." ¶ 14 of Dr. Triozzi's December 18, 1997 affidavit. Thus Appellants' invention encompasses the nonobvious recognition that lymph nodes excised from HIV patients are the source of a cell population suitable for treating HIV caused disease.

Thus, the command to determine obviousness in accordance with the *Graham v. John Deere* tripartite test highlights the shortfalls of the references cited:

> "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher."
>
> *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983).

The present invention demonstrates both surprising and unexpected efficacy by choosing infected lymph nodes from among the many potential sources of lymphocytes. Appellants' have presented clear, unrebutted evidence that no prior artisans could have recognized the advantages of the invention. Thus, neither the Babbitt citation nor the Ochoa citation renders obvious the present invention and Appellants have overcome these grounds for rejection.

2. The application in condition for allowance since the oath and declaration are in order and because the Application properly claims of priority.

Previously, a new declaration claiming priority to said applications was submitted with the signature of inventor Dr. Ridihalgh. A copy of the declaration with Dr. Olsen's signature was submitted August 30, 2004. The specification was amended in a paper submitted previously to claim priority to parent applications 08/604,728 and PCT 97/02309, and adopting the Examiner's phrase "a 371 of." Thus, so long as the amendments to the specification are entered, the Examiner's suggestions will have been adopted and Appellants request that these rejections be withdrawn on the grounds that they are moot.

Conclusion

Accordingly, Appellants respectfully urge the Board to overrule the rejection of the appealed claims and to permit the appealed application to pass to issue.

Respectfully submitted,

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APPENDIX

The Appealed Claims

Claims 1-28. (Cancelled)

29. (Previously Amended) An enriched T helper cell population expanded by subjecting cells derived from lymph nodes excised from patients infected with HIV to mitogenic stimulation in serum-free media for their expansion.

30. (Previously Amended) An enriched T helper cell population expanded by subjecting cells derived from lymph nodes excised from patients infected with HIV to mitogenic stimulation in serum-free media for their expansion, wherein said mitogenic stimulation includes the presence of Interleukin-2 (IL-2) and anti-CD3 monoclonal antibody.

31. (Previously Amended) An enriched T helper cell population expanded by subjecting cells derived from lymph nodes excised from patients infected with HIV to mitogenic stimulation in serum-free media for their expansion, wherein said mitogenic stimulation includes the presence of Interleukin-2 (IL-2) at about 600 IU/ml and anti-CD3 monoclonal antibody at between about 1 and 100 ng/ml.

32. (Previously Amended) An enriched T helper cell population expanded by subjecting cells derived from lymph nodes excised from patients infected with HIV to mitogenic stimulation in serum-free media for their expansion, wherein said mitogenic stimulation includes the presence of Interleukin-2 (IL-2) at about 600 IU/ml and anti-CD3 monoclonal antibody at between about 1 and 100 ng/ml, and wherein the amount of IL-2 is lowered to about 120 IU/ml after 7 days of expansion.

33. (Previously Amended) An enriched T helper cell population expanded by subjecting cells derived from lymph nodes excised from patients infected with HIV to mitogenic stimulation in serum-free media for their expansion, wherein said mitogenic stimulation includes the presence of Interleukin-2 (IL-2) at about 600 IU/ml and anti-CD3 monoclonal antibody at between about 1 and 100 ng/ml, wherein the amount of IL-2 is lowered to about 120 IU/ml after 7 days of

expansion, and wherein said expansion extends to at least about 10 days.

34. (Previously Amended) An enriched T helper cell population expanded by subjecting cells derived from lymph nodes excised from patients infected with HIV to mitogenic stimulation in serum-free macrophage media for their expansion, wherein said mitogenic stimulation includes the presence of Interleukin-2 (IL-2) at about 600 IU/ml and anti-CD3 monoclonal antibody at between about 1 and 100 ng/ml.

35. (Previously Amended) An enriched T helper cell population expanded by subjecting cells derived from lymph nodes excised from patients infected with HIV to mitogenic stimulation in serum-free macrophage media for their expansion, wherein said mitogenic stimulation includes the presence of Interleukin-2 (IL-2) and anti-CD3 monoclonal antibody.

Claims 36-41. (Cancelled)